Stability – The Current Status

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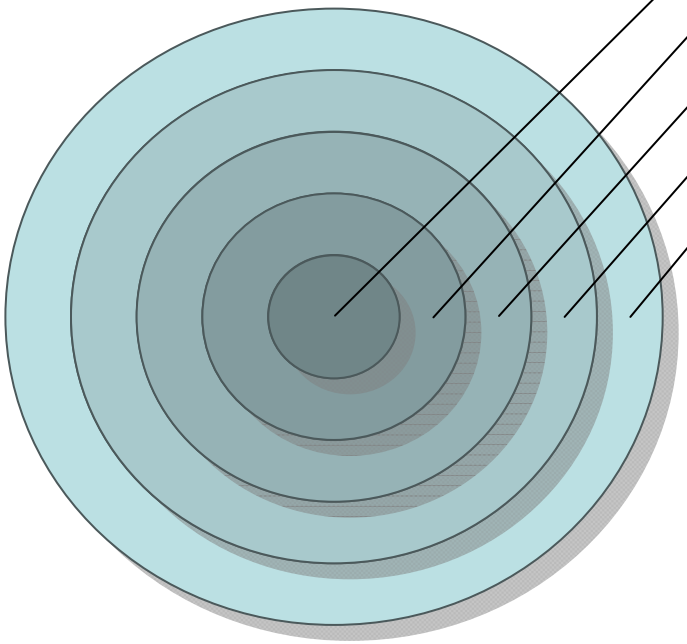
Where we are Today



Goal: Align stability expectations for ANDAs with ICH

2011/2012: Previewed ideas at GPhA Workshops and met with industry

September 25, 2012: Published draft Stability Guidance for ANDAs

June 20, 2013: Published final Stability Guidance for ANDAs

August 27, 2013: Published draft Q&A guidance with implementation date

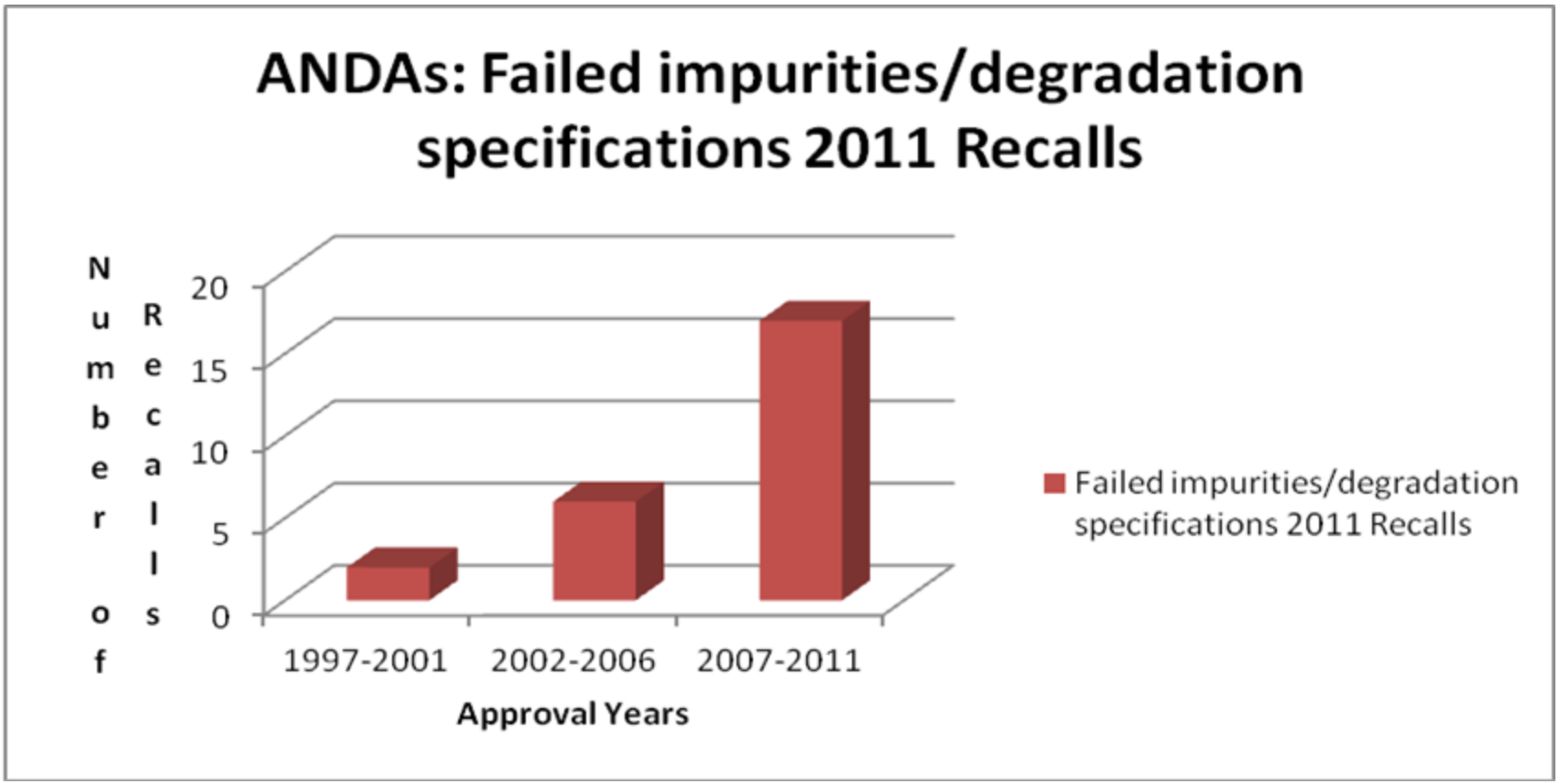
What led us here

- OGD in 2011
  - No formal guidance on stability expectations
  - Numerous stability related questions from industry that had to be handled on a case-by-case basis
  - Tremendous burden on OGD resources
  - Many requests asking about the applicability of ICH Q1A

What led us here

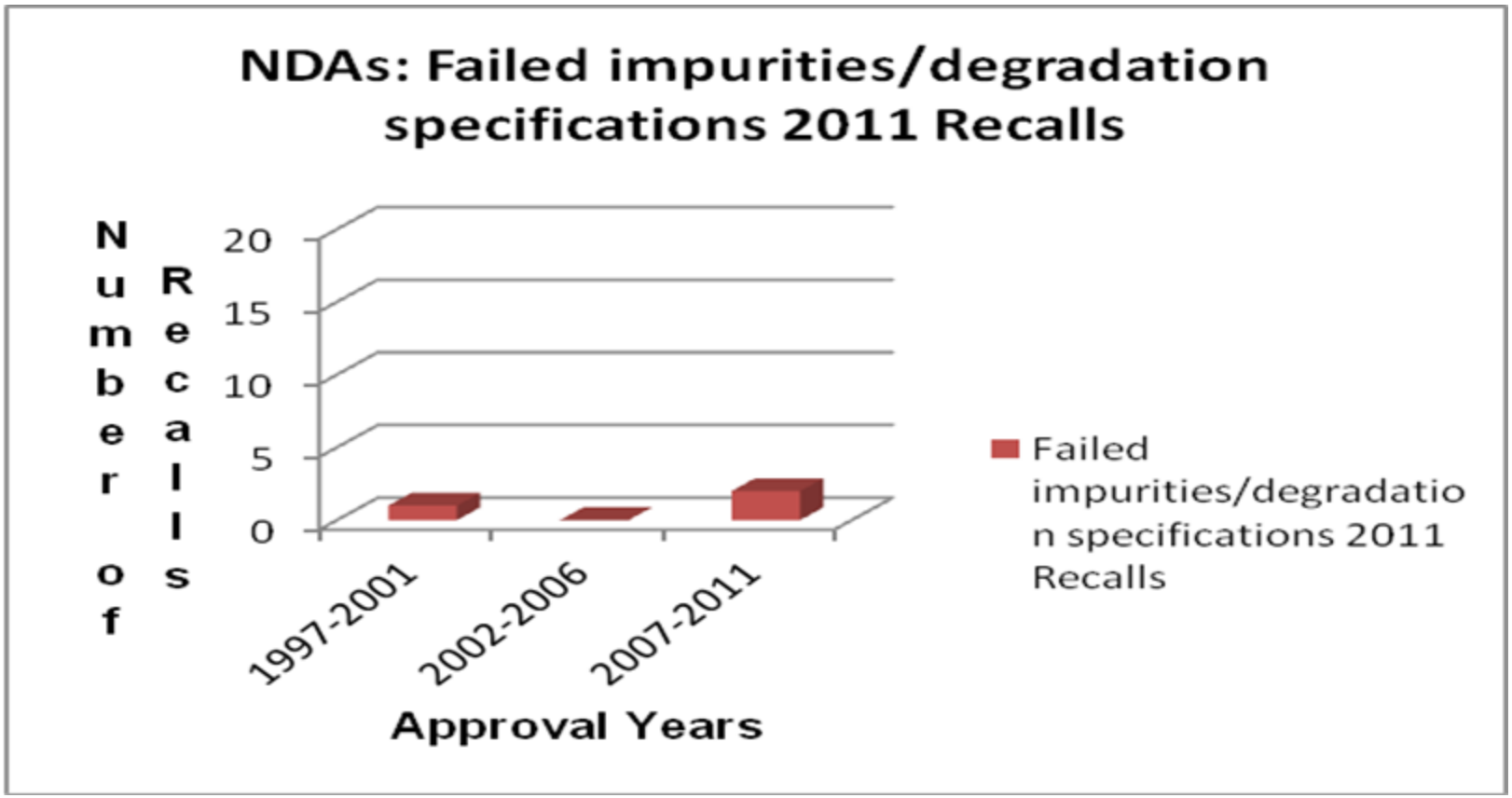
- OGD in 2011 (continued)
  - Determined ~35% of Field Alert Reports (FARs) were for stability failures, including
    - Out of Specification results for known degradants
    - Out of Specification results for unidentified degradants
    - Out of Specification results for total degradants
    - Dissolution failures
    - Reduced expiry dating
  - Received numerous supplements requesting expiry date reductions due to stability failures

What led us here



Prepared by Samia Nasr

What led us here



Prepared by Samia Nasr

What led us here

- OGD in 2011 (continued)
  - Stability related ICH documents had been adopted for new drug approval
  - Other international agencies in Europe, Canada, and Japan were using ICH Q1A-E guidelines for generic drug approval

What led us here

The time had come to adopt stability related ICH documents for generic drug approval!!!

What this meant for the Generic Industry

- The Stability Guidance for ANDAs (finalized on June 20, 2013) asks applicants to follow the stability recommendations provided in ICH Q1A-E guidelines

1. Data from 3 pilot scale batches, or 2 pilot batches and 1 small scale batch.

2. Six months accelerated and long-term data.

3. Multiple lots of drug substance.

4. Principles that are representative of the commercial process.

What this meant for the Generic Industry

5. Fully packaged primary exhibit batch

6. Three batches when using bracketing and matrixing designs

7. Statistical analysis of the data as appropriate

- Deviation from the recommendations should be justified.

What this meant for the Generic Industry

- The Question & Answer guidance (published in draft on August 27, 2013) provides clarification on questions about:
  - General issues
  - Drug master files
  - Drug product manufacturing and packaging
  - Amendments to pending ANDAs, and
  - Stability studies
- Specifies that the Stability Guidance for ANDAs
  - Covers all new ANDAs and Type II drug master files
  - Excludes post-approval changes

Industry was heard

- The original implementation date of January 2014 was revised to June 20, 2014, to give industry time to
  - Plan for necessary investments
  - Commit/allocate resources
  - Make organizational changes
  - Procure additional supplies/materials (e.g., active ingredients)
  - Produce additional batches of drug product, as necessary
  - Expand laboratory and stability storage capacities, as necessary

What will happen

- After implementation ANDAs not having the additional data recommended will be issued a Refuse-to-Receive (RTR) letter
- The ANDA filing checklist will be updated to specify 3 batches and 6 months stability data per the Stability Guidance for ANDAs
- Exceptions with justification may be considered for the following extreme situations:
  - A drug shortage ANDA
  - ANDAs that meet a specific U.S. Government need
  - ANDAs where the RLD has an orphan drug exemption
  - ANDAs that fall under the PEPFAR program or PET guidance recommendations
  - ANDAs using a controlled drug substance with limitations

What we gain

- Clarity in the stability expectations and a formal process for generic drugs that aligns with ICH.
- Harmonization between new and generic drugs, as well as internationally.
- An overall enhancement in the quality of generic drugs that benefits us all.

Acknowledgement

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Neeru Takiar

A very special thanks to industry!!!